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LAHIVE & COCKFIELD, LLP FLOOR 30, SUITE 3000 ONE POST OFFICE SQUARE BOSTON, MA 02109			BORQEEST, CHRISTINA M	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>
	10/813,324	TISSENBAUM ET AL.
	<b>Examiner</b> Christina Borgeest	<b>Art Unit</b> 1649

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) Responsive to communication(s) filed on 09 September 2008.  
 2a) This action is FINAL.      2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4) Claim(s) 1,2,4,7-9,14-26,33-45 and 48-56 is/are pending in the application.  
 4a) Of the above claim(s) 8 and 49-56 is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1,2,4,7,9,14-26,33-45 and 48 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on 29 March 2004 is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) Notice of References Cited (PTO-892)  
 2) Notice of Draftperson's Patent Drawing Review (PTO-948)  
 3) Information Disclosure Statement(s) (PTO/SB/08)  
 Paper No(s)/Mail Date \_\_\_\_\_

4) Interview Summary (PTO-413)  
 Paper No(s)/Mail Date \_\_\_\_\_

5) Notice of Informal Patent Application  
 6) Other: \_\_\_\_\_

**DETAILED ACTION**

***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9 September 2008 has been entered.

The Examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Christina Borgeest, Art Unit 1649.

***Formal Matters***

Claims 1, 2, 4, 7, 9, 14-16, 24-26, 33-36 and 45 are amended. Claims 3, 5, 6, 10-13, 27-32, 46 and 47 are cancelled. Claims 8 and 49-56 are withdrawn. Claims 1, 2, 4, 7, 9, 14-26, 33-45 and 48 are under examination.

***Rejections Withdrawn***

The rejections of claim 45 by Ruvkun et al. and Richardson et al. under 35 U.S.C. 102(b) are hereby withdrawn due to Applicants' amendment to require that the method recited in claim 45 be carried out in a "cell free assay composition."

***Maintained and New Objections/Rejections***

**Note** that the Response to Arguments section is found after all rejections

***Claim Objections***

Claim 45 is objected to because of the following informalities: The claim recites "contacting cell free-assay" in the beginning of third line, and presumably the article "a" should precede "cell free-assay." In addition, the claim recites "cell-fee" at the end of the third line, where presumably "cell-free" was intended. Appropriate correction is required.

Claim 48 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Since claim 45 now incorporates the limitation of a cell free assay composition, claim 48 no longer properly limits this claim.

***Claim Rejections - 35 USC § 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 33 recites the limitation "said insulin signaling pathway", and depends from claim 24. There is insufficient antecedent basis for this limitation in the claim, because claim 24 does not refer to an "insulin signaling pathway".

***Claim Rejections - 35 USC § 112, first paragraph – Written Description***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 9, 14-26, 33-45 and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation of "a mammalian orthologue" of various *C. elegans*

genes. Given the relatively low degree of sequence identity between *C. elegans* and mammalian genes, one of skill in the art at the time of the invention would not know when he/she was in possession of a mammalian orthologue of EGL-30, for example. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the *invention*. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the *C. elegans* genes and their encoded proteins that are recited in the claims, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to

be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only *C. elegans* genes and their encoded proteins, but not the full breadth of the claim (i.e., not "mammalian orthologues") meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

#### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 14-22, 24-26, 33-36, 38 and 39, 40 under 35 U.S.C. 102(b) as being anticipated by Ruvkun et al. (US Patent Application publication 2001/0029617, of record) is maintained for reasons of record and the following. The claims are drawn to a method for identifying an agent capable of enhancing longevity comprising contacting an organism having altered activity or expression of a cholinergic pathway molecule with a test agent, wherein said altered activity or expression of a cholinergic pathway leads to increased lifespan, assaying for the ability of the test agent to increase the lifespan of the organism with respect to control, wherein said organism also has altered activity or expression of an insulin signaling pathway molecule selected

from the group consisting of DAF-2, AAP-1, IRS, AGE-1 PDK-1, AKT-1, AKT-2 and DAF-18 or a mammalian ortholog thereof; or alternatively by monitoring the effect of the test agent on expression, intracellular level, extracellular level, activity, post translational modification interaction or cellular localization of muscarinic receptor, EGL-30, EGL-8, RIC-8, DAG, SNARE complex or UNC-13 or a mammalian ortholog thereof, or alternatively monitoring the effect of the test agent on indicators of both the cholinergic pathway molecule and the insulin pathway molecule, wherein the organism is *C elegans*.

Ruvkun et al. teach contacting organisms with test agents, assaying for the ability of the agent to affect an indicator of the pathway, and identifying said agents as enhancers of longevity. See specifically paragraphs [0443] - [0445], drawn to screens for isolating longevity therapeutics. See also claims 12-15 of Ruvkun et al., which recite a method for identifying a compound that is capable of increasing longevity of a cell or organism, comprising contacting a biological sample with a candidate compound and assaying said sample for PTEN-mediated lipid phosphatase activity (wherein PTEN is the mammalian ortholog of DAF-18), and wherein an increase in said activity indicates a compound capable of increasing longevity of a cell or organism, wherein said method further comprises assaying said compound in a cell which comprises a mutation in a daf-18 gene (thus encompassing an organism that has altered activity or expression of DAF-18—i.e. meeting the limitations of instant claim 9, for instance). Ruvkun et al. discuss the significance of DAF-2, AGE-1, DAF-18 (and others) and their mammalian homologs and their importance in metabolism and insulin signaling at paragraphs [0008]

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– [0011]. At paragraphs [0042] - [0044] Ruvkin et al. contemplate a nematode or mouse transgenic animal in which there is altered activity or expression of one of the DAF, AGE or AKT genes. At paragraphs [0162] - [0163] and Figure 46, Ruvkin clearly indicates that the insulin signaling pathway is immediately downstream of the cholinergic pathway. That is, the insulin signaling pathway is itself part of the cholinergic pathway, as binding of acetylcholine to the cholinergic receptor causes insulin release (see paragraph [0163]) and of course subsequent activation of the insulin pathway. A "pathway" does not have a specific definition in the art, but is understood to be a series of molecules which are all involved in a common function. Furthermore, at paragraphs [0406] – [0409], Ruvkin et al. teach that:

"[M]uscarinic agonists cause dauer recovery in both *C. elegans* and *A. caninum*, and that this recovery is specifically inhibited by the muscarinic antagonist atropine. The endogenous neurotransmitter at muscarinic receptors is acetylcholine, which in vertebrates functions at cholinergic synapses in both the peripheral and central nervous system...Acetylcholine has a wide variety of functions in vertebrate signaling including sympathetic and parasympathetic ganglion cells as well as the adrenal medulla, synapses within the central nervous system, and motor end plates on skeletal muscle innervated by somatic motoneurons...Muscarinic receptors are found in muscle, the autonomic ganglia, the central nervous system and secretory glands. These receptors couple to G proteins and signal on longer time scales than nicotinic receptors. Signaling can be either excitatory or inhibitory...The nicotinic receptor has been the primary focus of the studies on cholinergic signaling in the worm...Fewer studies, however, have been done on muscarinic signaling in *C. elegans*. Binding studies on crude homogenates of *C. elegans* have shown that they contain muscarinic receptors that have the potential to bind to the muscarinic ligands...Several potential muscarinic receptor homologues have been identified in the *C. elegans* genome sequence database...There are two different classes of muscarinic receptor agonists: choline esters and cholinomimetic alkaloids... Carbachol is a synthetic choline ester which mimics acetylcholine and acts at both muscarinic and nicotinic receptors in mammals...Atropine specifically inhibits mammalian muscarinic

responses...Since all of the drug-induced dauer recovery was inhibited by atropine, we concluded that this response was mediated by muscarinic signaling.

In other words, these paragraphs demonstrate that Ruvkun et al. antagonized muscarinic receptors (an indicator of the cholinergic pathway as recited in claim 14 and 24, for example) as well as an understanding of the interaction between the insulin and cholinergic pathways. In addition, the dauer stage of *C. elegans* is extensively studied because of its ability to live for extended periods of time (see Conclusion), and this paragraph explicitly states that muscarinic antagonism inhibits "dauer recovery." In other words, altered activity of muscarinic receptors through antagonism prevents the termination of the dauer stage, which is a stage characterized by the organism's ability to live for extended periods of time (i.e., increased lifespan). Furthermore, at paragraphs [0412] – [0413] teach the interconnection of the insulin and cholinergic pathways:

"In vertebrate insulin signaling, ***many studies link muscarinic and insulin signaling pathways*** (emphasis added). Both adrenergic and cholinergic fibers innervate secretory cells in the vertebrate islet of Langerhans Consistent with the suggestion that muscarinic inputs increase *C. elegans* insulin-like signaling, mammalian autonomic cholinergic fibers enhance insulin secretion. Pharmacological stimulation with acetylcholine or carbachol can induce insulin release both *in vivo* and *in vitro*. This induction is completely abolished by atropine, showing that it is mediated by activation of muscarinic receptors on the  $\beta$  cells...In mammalian systems, binding of acetylcholine to the  $\beta$  cell muscarinic receptor causes activation of sodium channels, which in turn leads to a change in membrane potential to induce insulin.

These data suggest the model shown in FIG. 46 for dauer recovery in *C. elegans*. When pheromone levels decrease and food levels increase, acetylcholine is secreted from an as yet unidentified neuron and binds to the muscarinic receptor on an insulin-like secreting neuron or other cell. This induces secretion of an insulin-like signal to in turn induce dauer recovery (FIG. 46). The lack of muscarinic induced dauer recovery

in daf-2 mutants suggest that the insulin-like dauer recovery signal acts via the DAF-2 receptor homologue. From analogy with the vertebrate studies, we suggest that a muscarinic signal causes an increase in insulin release that would bind to the DAF-2 receptor and activate downstream genes which promote dauer recovery.... We suggest that the secretory cells that express such an insulin-like gene [in *C. elegans*] will also express muscarinic receptors and be connected to food, pheromone, and temperature sensory neurons."

Given this passage, it is inherent in the teachings of Ruvkun et al., that they are measuring both the monitoring of indicators of cholinergic pathways (e.g., muscarinic receptors) and indicators of insulin signaling pathways (e.g., "we suggest that a muscarinic signal causes an increase in insulin release that would bind to the DAF-2 receptor and activate downstream genes which promote dauer recovery...."), as is recited in amended claims 15, 25 and 26, for example, and as is encompassed by claim 16. In the instant case, it is clear that Ruvkun et al. recognized the link between the cholinergic and insulin signaling pathways and that one could not be measured without the other, however, there is actually no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency) (MPEP 2112). Note *In re Swinehart*, 439 F.2d 210, 213, 169 USPQ 226 (CCPA1971) indicating that a more relaxed burden may apply to the examiner's establishing a *prima facie* case of inherency in making a prior

art rejection. In order for the examiner to assert inherency there must merely be a reasonable basis to believe that the feature is present in the prior art, thus shifting the burden to applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied upon. See also *In re Best*, 562 F.2d 1252, 195 USPQ 430, 443 (CCPA 1977); *In re Schreiber*, 128 F.3d 1473, 1478, 44 USPQ2d 1429 (Fed. Cir. 1997). Ruvkun et al. clearly teach the link between muscarinic and insulin signaling pathways and therefore it is inherent to their teachings that both pathways are affected and indicators of both pathways are measured. Ruvkun et al. also teach measurement of expression and activity of reporters such as GFP and luciferase (see paragraphs [0419] - [0422]) which meets the limitations of claims 33, 34 and 36. Ruvkun et al. also teach that GFP in particular can be used to determine subcellular localization of the labeled protein (see paragraph [0421]) which meets the limitations of claims 18, 20, and 35. The limitations of claims 21 -22 are met as Ruvkun et al. teach performing the assays on *C. elegans* nematodes. The limitations of claims 38 and 39 are met because Ruvkun et al. contemplate performing the invention in mammalian or human cells at paragraph [0045]. The limitation of claim 40 is met as the cells are not only derived from a nematode, they are in fact contained in a nematode.

The rejection of claims 14, 24, 33 - 34, 36, and 38 - 39 under 35 U.S.C. 102(b) as being anticipated by Pasricha (1994. Gut 35:1319 – 1321; of record) is maintained for reasons of record and the following.

The claims are drawn to methods wherein the intended uses of the methods are to find agents "capable of enhancing longevity". The claims do not require actual measurement of longevity, but rather require administering agents and measuring certain effects on the cholinergic system. Pasricha et al. teach methods of administering botulinum toxin, which prevents acetylcholine release and therefore is "an agent that inhibits the cholinergic pathway", to human patients. The "test agent" recited in independent claims 14 and 24 can be of any structure, thus botulinum toxin is reasonably "a test agent". Pasricha et al. teach assaying for the ability of the agent (i.e., botulinum toxin) to inhibit the cholinergic pathway by monitoring the activity of an indicator of the pathway. The indicators used were sphincter of Oddi pressure (description of how this pressure is measured appears at p. 1319 second column), biliary scintigraphy (p. 1319 last complete paragraph) and perceived pain (see Figure 1). The independent claims recite "monitoring the effect of the test agent on one or more of the expression, intracellular level, extracellular level, activity, post-translational modification, interaction or cellular localization of an indicator of said cholinergic pathway...wherein the indicator of said cholinergic pathway is selected from the group consisting of muscarinic receptor,...SNARE complex." Because Pasricha et al. teach administering an agent to an organism with a cholinergic pathway (which humans have), and they measure the ability of that agent to inhibit the cholinergic pathway, this can be reasonably interpreted as monitoring activity of an indicator of the cholinergic pathway. While Pasricha et al. do not explicitly teach monitoring the cholinergic pathway indicators recited in the independent claims, this is inherent to their methods

for the following reasons. Note that the mechanism of action of botulinum toxin is 1) to cleave the SNARE proteins 2) thus blockading the release of acetylcholine (see Conclusion). Blockading the release of acetylcholine also has the effect of changing the activity of the muscarinic receptors, since these receptors bind acetylcholine. Thus botulinum toxin acts by changing the activity of both SNARE proteins and muscarinic receptors. By measuring sphincter of Oddi pressure, biliary scintigraphy and perceived pain, Pasricha et al. were inherently measuring the **activity** of SNARE proteins and muscarinic receptors, because the mechanism of action of botulinum toxin requires the ability of the toxin to cleave the SNARE proteins and thus blockade the release of acetylcholine. Note also that there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency) (MPEP 2112). Note *In re Swinehart*, 439 F.2d 210, 213, 169 USPQ 226 (CCPA1971) indicating that a more relaxed burden may apply to the examiner's establishing a *prima facie* case of inherency in making a prior art rejection. In order for the examiner to assert inherency there must merely be a reasonable basis to believe that the feature is present in the prior art, thus shifting the burden to applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied upon. See also *In re Best*, 562 F.2d 1252, 195 USPQ

430, 443 (CCPA 1977); *In re Schreiber*, 128 F.3d 1473, 1478, 44 USPQ2d 1429 (Fed. Cir. 1997). Because botulinum toxin acts by cleaving the SNARE proteins thus blockading the release of acetylcholine, the teaching of the dependent measures reported in Pasricha et al. can be reasonably interpreted as a measure of the activity of the cholinergic pathway indicators, SNARE complex and muscarinic receptors. Pasricha teaches selecting the botulinum toxin, which inhibits the cholinergic pathway; see p. 1321 first complete paragraph which describes the authors' conclusion that "intraspincteric botulinum toxin injection seems to lower sphincter of Oddi pressure", which reasonably constitutes selecting the agent. While the reference does not explicitly discuss identifying the agents as being capable of enhancing longevity, such a step is not explicitly required by independent claims 14 and 24. Rather these claims end with a clause that constitutes an intended use of the method ("to thereby identify an agent"). The active method step only requires selecting an agent that inhibits the cholinergic pathway, which botulinum toxin does. As the prior art teaches every active step of claims 14 (drawn to contacting an organism with an agent) and 24 (drawn to contacting a cell with an agent), the reference anticipates the claimed invention. Claim 19 and 36 are rejected as the agent (botulinum toxin) is identified based on its ability to alter an activity of said indicator, which is explained above. Claims 38 - 39 are rejected as the cells are human.

The rejection of claims 14 and 24 under 35 U.S.C. 102(b) as being anticipated by Dunant et al. (1990. J. Physiol. Paris 84:211-219; of record) is maintained for reasons of

record and the following. Dunant et al. teach methods of administering botulinum toxin, which is an agent that inhibits acetylcholine release (p. 211 second column second paragraph; see also Conclusion), to fish and to cells taken from fish. Specifically, at p. 213 first complete paragraph Dunant et al. teach that large doses of botulinum toxin injected into Torpedo electric organ decreases the reflex electrical discharge from 65 V to 44 V. Since the electrical activity of the organ is clearly an indicator of the pathway activity, measuring the electrical discharge can be reasonably interpreted as measuring "the ability of the test agent to inhibit the cholinergic pathway by monitoring the effect of the test agent on... activity... of an indicator of said cholinergic pathway" as recited in claim 14. Dunant et al. compared the value to control as recited in claim 14 by simultaneously measuring the contralateral non-injected organ, whose discharge voltage did not change. Dunant et al. selected botulinum toxin for further experiments, as recited in claim 14. The final step recited in claim 14 ("to thereby identify an agent...") does not actually require additional steps and therefore can reasonably be construed as an intended use of the method. Dunant et al. clearly teach every step of the method of claim 14. Dunant et al. also teaches the method of claim 24. At p. 213 the reference teaches contacting cells (contained in prisms) from Torpedo electric organs with botulinum toxin and measuring the effect on voltage. The effect on voltage is reasonably an indicator of the cholinergic pathway. Dunant et al. also teach measuring the degree of synaptic release of acetylcholine, which is also within the scope of claim 24 (see Dunant, p. 215 second column). Dunant et al. teach selecting the botulinum toxin for further experimentation, including studying the effects on metabolic indicators. The final

step recited in claim 24 ("to thereby identify an agent...") does not actually require additional steps and therefore can reasonably be construed as an intended use of the method. Clearly Dunant et al. teach every step of claim 24. The reference teaches assaying for the ability of the test agent to affect the activity of acetylcholine, and teaches selecting botulinum toxin. While Dunant et al. do not explicitly teach monitoring the cholinergic pathway indicators recited in the independent claims, this is inherent to their methods for the following reasons. Note that the mechanism of action of botulinum toxin is 1) to cleave the SNARE proteins 2) thus blockading the release of acetylcholine (see Conclusion). Blockading the release of acetylcholine also has the effect of changing the activity of the muscarinic receptors, since these receptors bind acetylcholine. Thus botulinum toxin acts by changing the activity of both SNARE proteins and muscarinic receptors. By measuring electrical activity of the organ, Dunant et al. were inherently measuring the **activity** of SNARE proteins and muscarinic receptors, because the mechanism of action of botulinum toxin requires the ability of the toxin to cleave the SNARE proteins and thus blockade the release of acetylcholine. Note also that here is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency) (MPEP 2112). Note *In re Swinehart*, 439

F.2d 210, 213, 169 USPQ 226 (CCPA1971) indicating that a more relaxed burden may apply to the examiner's establishing a *prima facie* case of inherency in making a prior art rejection. In order for the examiner to assert inherency there must merely be a reasonable basis to believe that the feature is present in the prior art, thus shifting the burden to applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied upon. See also *In re Best*, 562 F.2d 1252, 195 USPQ 430, 443 (CCPA 1977); *In re Schreiber*, 128 F.3d 1473, 1478, 44 USPQ2d 1429 (Fed. Cir. 1997). Because botulinum toxin acts by cleaving the SNARE proteins thus blockading the release of acetylcholine, the teaching of the dependent measures reported in Dunant et al. can be reasonably interpreted as a measure of the activity of the cholinergic pathway indicators, SNARE complex and muscarinic receptors.

The rejection of claims 45 and 48 under 35 U.S.C. 102(b) as being anticipated by Richardson et al. (1991. Molecular Pharmacology 40:908-914; of record) is maintained. Richardson et al. teach assay compositions, which are cell-free and therefore within the scope of claims 45 and 48, comprising purified muscarinic receptors, which are cholinergic pathway molecules. Specifically, at p. 909 second complete paragraph the reference teaches assays to determine binding of ligand to the receptors. The results are described at p. 909 second column, where the authors indicate selecting those antibodies which modulate the ability of  $G_o$  to induce agonist binding to receptors. Richardson teaches selecting agents (i.e. antibodies) which inhibit the activity (G-protein signaling) of the receptor; see paragraph spanning pp. 910 - 911, which indicates

selection of the m4b antibodies. Thus the reference teaches all active steps of claim 45. The final step recited in claim 45 ("to thereby identify an agent...") does not actually require additional steps and therefore can reasonably be construed as an intended use of the method. Note that G proteins discussed in Richardson et al. are "mammalian orthologues" of EGL proteins recited in the claims.

Claims 45 and 48 are rejected under 35 U.S.C. 102(b) as being anticipated by Gusovsky et al. (European J Pharmacol. 1991; 206: 309-14). The claims encompass a method of contacting a cell-free assay composition with a test agent, wherein said cell-free assay composition comprises a cholinergic pathway molecule selected from the group consisting of EGL-30, EGL-3 and RIC-8, ***or a mammalian orthologue thereof***, and assaying for the ability of the test agent to affect the activity or expression of said cholinergic pathway molecule, thereby selecting an agent that inhibits the activity or expression of said cholinergic pathway molecule. The independent claim recites the preamble "a method for identifying an agent capable of enhancing longevity", which is an intended use of the method. The recitation of "to thereby" in the last line also reflects the intended use, and not an actual method step. Thus the claims encompass contacting a cell free system containing human guanine nucleotide binding protein with an agent which inhibits the activity of the GNBP.

Gusovsky et al. teach a cell free assay in which the amphilic peptides mastoparan and melittin inhibit guanine nucleotide-mediated phosphoinositide breakdown (see abstract):

In permeabilized HL-60 cells, mastoparan also inhibited phosphoinositide breakdown. Another amphiphilic peptide, melittin, was inactive in HL-60 intact cells, *but like mastoparan it inhibited guanine nucleotide-induced phosphoinositide breakdown in HL-60 cell membranes and permeabilized cells* (emphasis added). Thus, mastoparan peptides can stimulate phosphoinositide breakdown in intact HL-60 cells, probably through interactions with a guanine nucleotide binding protein. In permeabilized cells and in cell membranes, mastoparan inhibits guanine nucleotide-mediated phosphoinositide breakdown presumably through an interaction with an intracellular site.

In other words, in cell free systems, mastoparan peptides inhibited the ability of guanine nucleotide binding protein to mediate phosphoinositide breakdown. As explained above, the claims encompass contacting a cell free system containing human guanine nucleotide binding protein with an agent which inhibits the activity of the GNBP, thus the claims are anticipated by Gusovsky et al.

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 7 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruvkun et al. (US Patent Application 2001/0029617; of record), and further in view of Gems & Riddle (Genetics, 2000; 154: 1597-1610). The claims are drawn to a method for identifying an agent capable of enhancing longevity comprising contacting an organism having altered activity or expression of a cholinergic pathway molecule with a test agent, wherein said altered activity or expression of a cholinergic pathway leads to increased lifespan, assaying for the ability of the test agent to increase the lifespan of the organism with respect to control, wherein said organism also has altered activity or expression of an insulin signaling pathway molecule selected from the group consisting of DAF-2, AAP-1, IRS, AGE-1 PDK-1, AKT-1, AKT-2 and DAF-18 or a mammalian orthologue thereof.

The first factor to consider in making a rejection under 35 U.S.C. 103(a) is to determine the scope and contents of the prior art. Ruvkun et al. teach contacting organisms with test agents, assaying for the ability of the agent to affect an indicator of the pathway, and identifying said agents as enhancers of longevity. See specifically paragraphs [0443] - [0445], drawn to screens for isolating longevity therapeutics. See also claims 12-15 of Ruvkun et al., which recite a method for identifying a compound that is capable of increasing longevity of a cell or organism, comprising contacting a biological sample with a candidate compound and assaying said sample for PTEN-mediated lipid phosphatase activity (wherein PTEN is the mammalian ortholog of DAF-

18), and wherein an increase in said activity indicating a compound capable of increasing longevity of a cell or organism, wherein said method further comprises assaying said compound in a cell which comprises a mutation in a daf-18 gene (thus encompassing an organism that has altered activity or expression of DAF-18). Ruvkun et al. discuss the significance of DAF-2, AGE-1, DAF-18 (and others) and their mammalian homologs and their importance in metabolism and insulin signaling at paragraphs [0008] – [0011]. At paragraphs [0042] - [0044] Ruvkin et al. contemplate a nematode or mouse transgenic animal in which there is altered activity or expression of one of the DAF, AGE or AKT genes. At paragraphs [0162] - [0163] and Figure 46, Ruvkun et al. clearly indicate that the insulin signaling pathway is immediately downstream of the cholinergic pathway. That is, the insulin signaling pathway is itself part of the cholinergic pathway, as binding of acetylcholine to the cholinergic receptor causes insulin release (see paragraph [0163]) and of course subsequent activation of the insulin pathway. A "pathway" does not have a specific definition in the art, but is understood to be a series of molecules which are all involved in a common function. Furthermore, at paragraphs [0412] – [0413] teach the interconnection of the insulin and cholinergic pathways:

"In vertebrate insulin signaling, many studies link muscarinic and insulin signaling pathways. Both adrenergic and cholinergic fibers innervate secretory cells in the vertebrate islet of Langerhans. Consistent with the suggestion that muscarinic inputs increase *C. elegans* insulin-like signaling, mammalian autonomic cholinergic fibers enhance insulin secretion. Pharmacological stimulation with acetylcholine or carbachol can induce insulin release both *in vivo* and *in vitro*. This induction is completely abolished by atropine, showing that it is mediated by activation of muscarinic receptors on the  $\beta$  cells...In mammalian systems, binding of acetylcholine to the  $\beta$  cell muscarinic receptor causes activation of sodium

channels, which in turn leads to a change in membrane potential to induce insulin.

These data suggest the model shown in FIG. 46 for dauer recovery in *C. elegans*. When pheromone levels decrease and food levels increase, acetylcholine is secreted from an as yet unidentified neuron and binds to the muscarinic receptor on an insulin-like secreting neuron or other cell. This induces secretion of an insulin-like signal to in turn induce dauer recovery (FIG. 46). The lack of muscarinic induced dauer recovery in daf-2 mutants suggest that the insulin-like dauer recovery signal acts via the DAF-2 receptor homologue. From analogy with the vertebrate studies, we suggest that a muscarinic signal causes an increase in insulin release that would bind to the DAF-2 receptor and activate downstream genes which promote dauer recovery.... We suggest that the secretory cells that express such an insulin-like gene [in *C. elegans*] will also express muscarinic receptors and be connected to food, pheromone, and temperature sensory neurons."

Ruvkun et al. meet the limitations of claim 7 because they teach an organism (*C. elegans*) with altered activity or expression of a cholinergic pathway molecule that is downstream from diacylglycerol or DAG. At paragraph [0224], they teach a mutation of AKT-1. It is further explained that AKT-1 has its closest non-AKT homolog to rat PKC, to which it shares 38% homology. PKC is downstream from DAG, thus the limitations of claim 7 are met. Ruvkun et al. teach measurement of expression and activity of reporters such as GFP and luciferase (see paragraphs [0419] - [0422]). Ruvkun et al. also teach that GFP in particular can be used to determine subcellular localization of the labeled protein (see paragraph [0421]). The second factor is to ascertain the differences between the prior art and the instant claims. Ruvkun et al. do explicitly not disclose that the altered expression or activity of the cholinergic pathway molecule leads to increased lifespan. Gems and Riddle teach mutations in pathway molecules that lead to increased lifespan (see, for example, p. 1601; also Figure 4). Gems and Riddle

also teach at p. 1602, right column: "several genes identified in *C. elegans* have a dual role in regulating dauer larva development and adult longevity... The dauer larva is a long-lived, developmentally arrested alternative third larval stage, which forms under conditions of starvation and crowding." Gems and Riddle indicate again at p. 1608, left column, 3<sup>rd</sup> paragraph, that mutations in DAF-2 and AGE-1 lead to increased lifespan in *C. elegans*. Finally, Gems and Riddle teach assaying for the ability of environment and behavior to increase the lifespan of organism with mutated genes (in which said mutations lead to increased lifespan) with respect to control. In summary, Ruvkun et al. provide the blueprint to the person of ordinary skill at the time the invention was made for designing longevity studies in *C. elegans* involving assaying for the ability of a test agent to increase lifespan. These teachings are explicit in the disclosure of Ruvkun et al. Furthermore, the extensive discussion concerning genetic mutations and their effect on *C. elegans* lifespan found in Gems and Riddle indicate that the skill in the art concerning knowledge of *C. elegans* mutations that lead to increased lifespan was high. In other words, given the teachings of Gems and Riddle, the person of ordinary skill in the art would know that the mutations in discussed in Ruvkun et al. can lead to increased lifespan. Furthermore, Gems and Riddle describe experiments evaluating the effects of genes, environment and behavior on lifespan and the mechanism of increased lifespan as a result of genetic mutations, indicating that the person of ordinary skill in the art would understand and appreciate how such mutations can be used in longevity studies. Ruvkun et al. already teach mutations described by Gems and Riddle, and Gems and Riddle provide guidance to the person of ordinary skill in the art

that such mutations extend lifespan. The person of ordinary skill in the art would merely be combining prior art elements according to known methods to achieve predictable results. Both references teach studies in which endpoints affecting lifespan are evaluated. The combining of these known elements would not be a result of true innovation but one of ordinary skill and common sense.

Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ruvkun et al. (US Patent Application 2001/0029617; of record) as applied to claims 14, 21-22, 24-26, 33-36, 38 and 39, 40. The reasons why claims 14, 21-22, 24-26, 33-36, 38 and 39, 40 are anticipated by Ruvkun et al. are set forth above and are hereby incorporated.

The first factor to consider in making a rejection under 35 U.S.C. 103(a) is to determine the scope and contents of the prior art. Ruvkun et al. teach longevity screening assays using the nematode *C. elegans*, which is explained in greater detail in the rejection above under 35 U.S.C. 102(b), and is hereby incorporated. Ruvkun et al. also teach using the parasitic nematode *A. caninum* in different screening assays such as for finding nematicides and teaches the similarity of the biochemical pathways in *C. elegans* and *A. caninum*, and thus is on point to claim 23. The second factor is to ascertain the differences between the prior art and the instant claims. Ruvkun et al. do explicitly not disclose carrying out the longevity screening assays in the parasitic nematode, *A. caninum*. Nevertheless, it would have been obvious to one of ordinary

skill in the art to perform the screening assays for longevity-enhancing compounds taught by Ruvkun et al. on parasitic nematodes, with a reasonable expectation of success. The motivation to do so would be to find longevity-enhancing compounds. It would be reasonable to expect success, as Ruvkun et al. teach that the biochemical pathways found in *C. elegans* are also present in the parasitic nematode *A. caninum*, and the level of ordinary skill in the art is high, as evidenced by Ruvkun et al. Finally, It is obvious to substitute one screening organism for another as both were known .to be similarly suitable for the same purpose in the prior art; see MPEP § 2144.06. The claim would have been obvious because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art; this substitution is not a result of true innovation but one of ordinary skill and common sense.

Claims 20 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruvkun et al. (US Patent Application 2001/0029617; of record) as applied to claims 1, 2, 4, 7, 9, 14-19, 21-22, 24-26, 33-36, 38 and 39-44). The reasons why claims (US Patent Application 2001/0029617) as applied to claims 1, 2, 4, 7, 9, 14-19, 21-22, 24-26, 33-36, 38 and 39-44 are anticipated by Ruvkun et al. are set forth in the rejection under 35 USC 102 above. The first factor to consider in making a rejection under 35 U.S.C. 103(a) is to determine the scope and contents of the prior art. Ruvkun et al. teach screening assays with the scope of those claims using the nematode *C. elegans*. Ruvkun et al. also teach that when performing other screening assays, agents can be identified based on their ability to alter sub-cellular localization of indicators such as

GFP fusion proteins (see for example paragraphs [0242], [0319] - [0326], and [0421]). The second factor is to ascertain the differences between the prior art and the instant claims. Ruvkun et al. do not explicitly teach monitoring the ability of agents to alter cellular localization of indicators, as recited in claims 20 and 37, while performing the screening assays set forth in independent claims 14, 15 or 24-26. Nevertheless, it would have been obvious to one of ordinary skill in the art to monitor cellular localization of indicators when performing the assays taught in Ruvkun et al. with a reasonable expectation of success. The motivation to do so would be to accurately monitor which genes are active within the cell, and within which portions of cells, which Ruvkun teaches is a useful way to identify drugs. See particularly paragraph [0421] which teaches that monitoring cellular localization is useful in identifying targets for diabetes, which is related to the insulin signaling pathways. Finally, it is obvious to substitute monitoring cellular localization as a measure inhibition of cholinergic pathway activity as this method was known in the art and discussed by Ruvkun et al. to be useful for identifying drugs. The claim would have been obvious because the substitution of one known element for another in a method claim would have yielded predictable results to one of ordinary skill in the art; this substitution is not a result of true innovation but one of ordinary skill and common sense.

***Response to Arguments***

1. Applicants' arguments in remarks filed 8 September 2008 can be summarized in the following way. Applicants argue that the references (Ruvkun et al.; Pasricha et al.;

Dunant et al.; Richardson et al.) fail to teach every limitation of the claimed invention. Specifically, Applicants argue that the references do not teach screening assays to identify modulators of the cholinergic pathway as now recited in amended claim 14, for example (i.e., "wherein the indicator of said cholinergic pathway is selected from the group consisting of muscarinic receptor, EGL-30, EGL8, RIC-8, DAG, SNARE complex and UNC-13) and do not teach a method of identifying an agent capable of enhancing longevity.

2. With regard to Ruvkun et al., Applicants argue further that "the teachings of Ruvkun related to the cholinergic pathway are limited to experiments involving contacting *C. elegans* with a known agonist of the muscarinic receptor and monitoring the single readout of dauer formation", and does not teach screening assays for the identification of inhibitors of the cholinergic pathway.
3. With regard to rejections made under 35 U.S.C. 103(a), Applicants did not traverse the examiner's determination based on the conclusion that the primary reference by Ruvkun et al. does not anticipate the base claims and therefore cannot serve as a primary reference under 35 USC 103. Specifically, they argue that one of skill in the art would not have had a reasonable expectation of success, based on the disclosure of Ruvkun et al. to arrive at the claimed invention because the teachings of Ruvkun related to the cholinergic pathway are limited to experiments involving contacting *C. elegans* with an agonist of the muscarinic receptor and monitoring the single readout of dauer formation. Applicants further argue that dauer formation and enhanced life span are completely different phenotypes and that absent the teachings of the present invention which clearly link the inhibition of the cholinergic pathway with increased lifespan, there would have been no reasonable expectation of success in identifying agents that increase longevity using the presently claimed assays.

Regarding arguments number 1 and 2 made concerning Ruvkun et al., these have been fully considered but is not found persuasive for the following reasons. First, Ruvkin et al., which recite a method for identifying a compound that is capable of increasing longevity of a cell or organism, comprising contacting a biological sample with a candidate compound and assaying said sample for PTEN-mediated lipid phosphatase activity (wherein PTEN is the mammalian ortholog of DAF-18), and wherein an increase in said activity indicating a compound capable of increasing longevity of a cell or organism, wherein said method further comprises assaying said

compound in a cell which comprises a mutation in a daf-18 gene (thus encompassing an organism that has altered activity or expression of DAF-18). Second, Ruvkun et al. describe studies of dauer recovery in which the exit from dauer stage is prevented by the muscarinic antagonist, atropine. As explained above, the dauer stage represents a stage in which the nematode has an extended lifespan, thus meeting the limitations of the claims (altered activity of muscarinic receptor resulting in extended lifespan).

Ruvkun et al. also contemplate a nematode or mouse transgenic animal in which there is altered activity or expression of one of the DAF, AGE or AKT genes (i.e., the insulin pathway molecules recited in claims 2 and others). The claims are broad, and encompass "monitoring the effect of the test agent on **one or more** of the...activity,...interaction...of...muscarinic receptor..." In other words, Ruvkun et al. teach a method that is a blueprint for assaying agents that promote longevity in a test organism that has altered expression of an insulin signaling pathway molecule and measuring the activity and/or interaction of the muscarinic receptor. There is nothing in the claims that require the test agents be unknown. Furthermore, Ruvkun et al. do teach a screening assay and selection of agents based upon the ability to enhance longevity. Finally, as explained above, the cholinergic pathway is continuous with the insulin signaling pathway. Thus by measuring outputs and indicators of the insulin signaling pathway, Ruvkun et al. is also measuring outputs of the cholinergic pathway, as acetylcholine signaling activates insulin signaling. The claims are broad and the limitations are captured by Ruvkun et al.

Regarding argument 1 concerning Pasricha, as stated above, Pasricha et al. teach assaying for the ability of the agent (i.e., botulinum toxin) to inhibit the cholinergic pathway by monitoring the activity of an indicator of the pathway. The indicators used were sphincter of Oddi pressure, biliary scintigraphy and perceived pain. The independent claims recite "monitoring the effect of the test agent on one or more of the expression, intracellular level, extracellular level, activity, post-translational modification, interaction or cellular localization of an indicator of said cholinergic pathway...wherein the indicator of said cholinergic pathway is selected from the group consisting of muscarinic receptor,...SNARE complex." Because Pasricha et al. teach administering an agent to an organism with a cholinergic pathway (which humans have), and they measure the ability of that agent to inhibit the cholinergic pathway, this can be reasonably interpreted as monitoring activity of an indicator of the cholinergic pathway. While Pasricha et al. do not explicitly teach monitoring the cholinergic pathway indicators recited in the independent claims, this is inherent to their methods for the following reasons. Note that the mechanism of action of botulinum toxin is 1) to cleave the SNARE proteins 2) thus blockading the release of acetylcholine (see Conclusion). Blockading the release of acetylcholine also has the effect of changing the activity of the muscarinic receptors, since these receptors bind acetylcholine. Thus botulinum toxin acts by changing the activity of both SNARE proteins and muscarinic receptors. By measuring sphincter of Oddi pressure, biliary scintigraphy and perceived pain, Pasricha et al. were inherently measuring the **activity** of SNARE proteins and muscarinic receptors, because the mechanism of action of botulinum toxin requires the ability of the

toxin to cleave the SNARE proteins and thus blockade the release of acetylcholine. As stated above, there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency) (MPEP 2112). Note *In re Swinehart*, 439 F.2d 210, 213, 169 USPQ 226 (CCPA1971) indicating that a more relaxed burden may apply to the examiner's establishing a *prima facie* case of inherency in making a prior art rejection. In order for the examiner to assert inherency there must merely be a reasonable basis to believe that the feature is present in the prior art, thus shifting the burden to applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied upon. See also *In re Best*, 562 F.2d 1252, 195 USPQ 430, 443 (CCPA 1977); *In re Schreiber*, 128 F.3d 1473, 1478, 44 USPQ2d 1429 (Fed. Cir. 1997). Because botulinum toxin acts by cleaving the SNARE proteins thus blockading the release of acetylcholine, the teaching of the dependent measures reported in Pasricha et al. can be reasonably interpreted as a measure of the activity of the cholinergic pathway indicators, SNARE complex and muscarinic receptors.

Regarding argument 1 concerning Dunant et al., while Dunant et al. do not explicitly teach monitoring the cholinergic pathway indicators recited in the independent

claims, this is inherent to their methods for the following reasons. Note that the mechanism of action of botulinum toxin is 1) to cleave the SNARE proteins 2) thus blockading the release of acetylcholine (see Conclusion). Blockading the release of acetylcholine also has the effect of changing the activity of the muscarinic receptors, since these receptors bind acetylcholine. Thus botulinum toxin acts by changing the activity of both SNARE proteins and muscarinic receptors. By measuring electrical activity of the organ, Dunant et al. were inherently measuring the **activity** of SNARE proteins and muscarinic receptors, because the mechanism of action of botulinum toxin requires the ability of the toxin to cleave the SNARE proteins and thus blockade the release of acetylcholine. Note also that here is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency) (MPEP 2112). Note *In re Swinehart*, 439 F.2d 210, 213, 169 USPQ 226 (CCPA1971) indicating that a more relaxed burden may apply to the examiner's establishing a *prima facie* case of inherency in making a prior art rejection. In order for the examiner to assert inherency there must merely be a reasonable basis to believe that the feature is present in the prior art, thus shifting the burden to applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied upon. See also *In re Best*,

562 F.2d 1252, 195 USPQ 430, 443 (CCPA 1977); *In re Schreiber*, 128 F.3d 1473, 1478, 44 USPQ2d 1429 (Fed. Cir. 1997). Because botulinum toxin acts by cleaving the SNARE proteins thus blockading the release of acetylcholine, the teaching of the dependent measures reported in Dunant et al. can be reasonably interpreted as a measure of the activity of the cholinergic pathway indicators, SNARE complex and muscarinic receptors.

Regarding argument 1 concerning Richardson, G proteins discussed in Richardson et al. are "mammalian orthologues" of EGL proteins recited in the claims.

Regarding argument 3 concerning Ruvkun et al., the Examiner is not persuaded that dauer formation and enhanced life span are completely different phenotypes. First, on the contrary, it is the characteristic of the dauer phenotype to survive for long periods of time that makes it interesting to biologists (see Conclusion). Second, the claims are broad, and the endpoint of measuring how a muscarinic antagonist (atropine) prevents exit from the dauer stage in *C. elegans* can be reasonably interpreted as an endpoint in longevity studies. Third, as discussed above, Ruvkun et al. clearly teach the link between the insulin pathway and increased lifespan and the link between the insulin and cholinergic pathways. Fourth, the fact that Applicants have recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). In other words,

claims 20 and 37 were found to be obvious because cellular localization is a recognized substitute endpoint in a study and claim 23 was found to be obvious because a parasitic nematode is a recognized substitute for a test organism. The methods were anticipated; the only obvious elements that one of skill in the art would need to apply his or her knowledge would be to substitute these known elements in the method claims to achieve predictable results. Finally, the claims are extremely broad, and claims 14-26, 33-45 and 48 do even not require the knowledge of a link or connection between the cholinergic pathway and lifespan. The active method steps only require selecting an agent that inhibits the activity or expression of one or more of the recited cholinergic pathway molecules, which Ruvkun et al. clearly teach. Ruvkun et al. measured muscarinic receptors (an indicator of the cholinergic pathway as recited in claim 14, 15, 24, 25 and 26) as well as an understanding of the interaction between the insulin and cholinergic pathways. Altered activity of muscarinic receptors through antagonism by atropine prevents the termination of the dauer stage, which is a stage characterized by the organism's ability to live for extended periods of time (i.e., increased lifespan). For this reason, the limitations of the claims requiring altered activity or expression of a cholinergic pathway molecule leading to increased lifespan are met (including claim 4, because a study in which muscarinic receptors are antagonized meets the limitations of "altered activity").

***Conclusion***

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Borodic et al. (Expert Opin Investig Drugs. 2001; 10: 1531-44) teach the mechanism of action of botulinum toxin and its effect on the SNARE complex; see for example at p. 1532). In addition, See Tatar and Yin, Experimental Gerontology; 2001; 36: 723-738, who discuss the study of diapause (or dauer formation in *C. elegans*), and its relevance for the study of aging and senescence.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is (571)272-4482. The examiner can normally be reached on 8:00am - 2:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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